Exhibit A

DEFENDANTS' MOTION FOR LEAVE TO FILE
A MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG,	:	C.A. No. 1:13-cv-00052-RGA
Plaintiffs,	:	
v.	:	
ALVOGEN PINE BROOK, INC. and ALVOGEN GROUP, INC.,	:	
Defendants.	:	

DEFENDANTS' MOTION FOR
SUMMARY JUDGMENT OF NONINFRINGEMENT

Defendants Alvogen Pine Brook, Inc. and Alvogen Group Inc. (collectively, "Alvogen") respectfully request leave of the Court to file a motion for summary judgment of noninfringement of U.S. Patents No. 6,355,031 ("the '031 patent") and 6,316,023 ("the '023 patent") in C.A. No. 1:13-cv-00052-RGA, which pertains to Alvogen's Abbreviated New Drug Application ("ANDA") for a rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosage strengths ("Alvogen's ANDA Products").

As set out more fully in the Memorandum of Law accompanying this motion, each and every claim of the '031 and '023 patents requires an antioxidant. To prove infringement, Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd. and LTS Lohmann Therapie-Systeme AG (collectively, "Plaintiffs") must therefore prove that the ANDA Products contain an antioxidant. Alvogen's ANDA states that the ANDA Products do not contain an antioxidant. During fact discovery, Plaintiffs stated that future testing by their experts would demonstrate the presence of an

antioxidant in the ANDA Products. Plaintiffs did not provide any expert report to Alvogen by the May 2, 2014 deadline, however, and thus cannot carry their burden of proof. Summary judgment of noninfringement is therefore appropriate.

WHEREFORE, Alvogen respectfully requests that the Court grant its motion for summary judgment of noninfringement.

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Exhibit B

DEFENDANTS' MOTION FOR LEAVE TO FILE
A MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG,	:	C.A. No. 1:13-cv-00052-RGA
Plaintiffs,	:	
v.	:	
ALVOGEN PINE BROOK, INC. and ALVOGEN GROUP, INC.,	:	
Defendants.	:	

MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

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Defendants Alvogen Pine Brook, Inc. and Alvogen Group Inc. (collectively, "Alvogen") respectfully submit this memorandum of law in support of their Motion for Summary judgment of Noninfringement of U.S. Patents No. 6,355,031 ("the '031 patent") and 6,316,023 ("the '023 patent").

Alvogen's Motion pertains only to the infringement allegations in the Complaint filed in C.A. No. 1:13-cv-00052-RGA by Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd. and LTS Lohmann Therapie-Systeme AG (collectively, "Plaintiffs"). In this Complaint, Plaintiffs allege that Alvogen infringed the '031 and '023 patents by filing an Abbreviated New Drug Application ("ANDA"), seeking approval to engage in the commercial manufacture, use, and sale of a rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosage strengths ("Alvogen's ANDA Products").[1]

ARGUMENT

Each and every claim of the '031 and '023 patents requires an antioxidant.[2] To prove infringement, Plaintiffs must therefore prove that the ANDA Products contain an antioxidant. Alvogen's ANDA states that the ANDA Products do not contain an antioxidant. During fact discovery, Plaintiffs stated that future testing by their experts would demonstrate the presence of an antioxidant in the ANDA Products. Plaintiffs did not provide any expert report to Alvogen by

[1] This motion for summary judgment does not pertain to the related C.A. No. 1:13-cv-00370-RGA, which involves Alvogen's higher-dose 13.3 mg/24 hr rivastigmine transdermal system. On May 3, 2014, Plaintiffs provided Alvogen with a covenant not to sue that covers the 13.3 mg/24 hr product. (Declaration of Thomas K. Hedemann ("Hedemann Decl."), Ex. 1.) The parties have agreed to a voluntary dismissal of all claims and counterclaims in that matter. Therefore, upon the entry of summary judgment of noninfringement here, Alvogen will not be a party to any suit involving the '031 and '023 patents.

[2] The Court has construed "antioxidant" to mean "agent(s) that reduce(s) oxidative degradation (presence only)." (D.I. 147, at 2.)

the May 2, 2014 deadline, however, and thus cannot carry their burden of proof. Summary judgment of noninfringement is therefore appropriate.

I. LEGAL STANDARDS

Summary judgment is a procedural tool that avoids wasteful trials when no genuine issue of material fact exists. Pure Gold, Inc. v. Syntex (U.S.A.), Inc., 739 F.2d 624, 626 (Fed. Cir. 1984). A court should grant summary judgment when "there is no genuine issue as to any material fact and [] the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56. See also Celotex Corp. v. Catrett, 477 U.S. 317, 322-23 (1986). This is the case when the non-moving party fails to present "sufficient evidence . . . for a jury to return a verdict for that party." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 249 (1986).

Patent infringement analysis involves two steps: (1) claim construction; and (2) application of the properly construed claims to the accused product. Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995). A patent claim is infringed only where the patentee shows that each and every claim limitation is found – literally or by equivalents – in the accused device. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 29 (1997). Thus, "[t]he failure to meet a single limitation is sufficient to negate infringement of the claim." Laitram Corp. v. Rexnord, Inc., 939 F.2d 1533, 1535 (Fed. Cir. 1991).

II. ALVOGEN IS ENTITLED TO SUMMARY JUDGMENT OF NONINFRINGEMENT BECAUSE PLAINTIFFS CANNOT PROVE THAT ALVOGEN'S ANDA PRODUCTS CONTAIN AN ANTIOXIDANT.

To prove that Alvogen's ANDA Products infringe any claim of the '031 or '023 patents, Plaintiffs must prove that the ANDA Products contain an antioxidant. Alvogen's ANDA states on its face that the ANDA Products do not contain an antioxidant. Plaintiffs therefore pointed to future expert testing of the components in the ANDA Products to identify an antioxidant.

Plaintiffs did not provide any expert report to Alvogen, however, and therefore cannot carry their burden of proof.

A. Every Claim of the '031 and '023 Patents Requires an Antioxidant.

Each of the three independent claims of the '031 patent requires an antioxidant:

> Claim 1. A pharmaceutical composition comprising: (a) a therapeutically effective amount of (S)-N-ethyl-3-(1-dimethylamino)ethyl-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A); *(b) about 0.01 to about 0.5 percent by weight of an antioxidant*, based on the weight of the composition, and (c) a diluent or carrier.
>
> Claim 11. A transdermal device comprising a backing layer, a layer comprising a therapeutically effective amount of (S)-N-ethyl-3-(1-dimethylamino)ethyl-N-methyl-phenyl-carbamate (Compound A) and *an amount of antioxidant effective to stabilize Compound A from degradation in a polymer matrix*, a release-liner and, disposed between the layer comprising Compound A in a polymer matrix and the release-liner, a discrete layer of adhesive material for releasably fixing said transdermal device to a patient's skin.
>
> Claim 15. A method of stabilizing (S)-N-ethyl-3-(1-dimethylamino)ethyl-N-methyl-phenylcarbamate in free base or acid addition salt form (Compound A), wherein the method comprises forming a composition by combining Compound A with *an amount of antioxidant effective to stabilize Compound A from degradation*.

('031 patent, Claims 1, 11 and 15, Hedemann Decl., Ex. 2, emphasis added.)

Each of the three independent claims of the '023 requires an antioxidant:

> Claim 1. A pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl phenyl carbamate in the form of a free base or acid addition salt, *0.01 to 0.5 weight percent of an antioxidant*, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.
>
> Claim 6. A pharmaceutical composition comprising 7 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl phenyl carbamate in the form of a free base; 10 to 30 weight percent of polymethacrylate or acid addition salt*; 0.05 to 0.3 weight percent of α-tocopherol*,[3] wherein the weight percents are based on the total weight of the composition.

[3] α-tocopherol is an antioxidant. ('031 patent, Col. 4, ll. 10-15, Hedemann Decl., Ex. 2.)

> Claim 7. A transdermal device comprising a pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl phenyl carbarnate in the form of a free base or acid addition salt, *0.01 to 0.5 weight percent of an antioxidant*, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

('023 patent, Claims 1, 6 and 7, Hedemann Decl., Ex. 3, emphasis added.)

Because every independent claim of the '031 and '023 patents requires an antioxidant, every dependent claim in the each patent also requires an antioxidant.

B. Alvogen's ANDA Provides that the ANDA Products Do Not Contain an Antioxidant.

Alvogen's ANDA provides an Ingredient Comparison with the Reference Listed Drug ("RLD"), i.e., Plaintiffs' Exelon patch, 4.6 mg/24 hr and 9.5 mg/24 hr. (Hedemann Decl., Ex. 4.) It provides that whereas the RLD contains the antioxidant alpha-tocopherol, Alvogen's ANDA Products do not contain an antioxidant. Thus, on the face of the ANDA, Alvogen's ANDA Products do not infringe any claim of the '031 or '023 patents.

C. Plaintiffs Cannot Prove that Alvogen's ANDA Products Contain an Antioxidant.

Plaintiffs served their Initial Infringement Contentions on May 28, 2013. (Hedemann Decl., Ex. 5.) These Contentions must state how the accused product meets each element of each asserted claim. With respect to the antioxidant element, Plaintiffs did not identify an antioxidant in the ANDA Products but stated that "Plaintiffs have requested samples of Alvogen's ANDA Products for testing to identify and quantify the antioxidant(s) and will provide supplemental responses upon the completion of those tests." (Id. at 2-9, 11-13.)

On November 7, 2013, Alvogen served four contention interrogatories on Plaintiffs directed to the antioxidant limitations. (Hedemann Decl., Ex. 6.) Plaintiffs objected that each interrogatory was premature, stating that "analyses and testing of the ingredients, components and portions of Alvogen's ANDA Products is ongoing . . . . Plaintiffs will describe in detail the

facts on which they rely for their infringement contentions in their expert reports, which they will produce to Alvogen in accordance with the Court's Scheduling Order." (Hedemann Decl., Ex. 7.)

During a meet-and-confer on March 17, 2014, Plaintiffs confirmed that they "do not possess any information beyond what is disclosed in Plaintiffs' infringement contentions and interrogatory responses . . . . [and] could not identify a factual basis for asserting that any specific ingredient, component or portion of . . . Alvogen's . . . ANDA Products literally infringe the 'antioxidant' limitation of the asserted claims, beyond referring [Alvogen] to [Plaintiffs'] contentions and interrogatory responses." (Hedemann Decl., Ex. 8.)

The deadline for Plaintiffs to provide an expert report to Alvogen was May 2, 2014. (D.I. 151.) Plaintiffs did not provide any expert report to Alvogen, providing instead a Covenant Not to Sue. (Hedemann Decl., Ex. 1.) Plaintiffs are therefore foreclosed from proving that Alvogen's ANDA Products contain an antioxidant, and consequently cannot meet their burden of proving that each and every element of the claims of the '031 and '023 patents are present in the ANDA Products. The Court should therefore grant Alvogen's motion for summary judgment of noninfringement.

CONCLUSION

For the foregoing reasons, the Court should grant Alvogen's motion for summary judgment of noninfringement.

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Dated: May 29, 2014

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG,	:	C.A. No. 1:13-cv-00052-RGA
Plaintiffs,	:	**CONFIDENTIAL - FILED UNDER SEAL**
v.	:	
ALVOGEN PINE BROOK, INC. and ALVOGEN GROUP, INC.,	:	
Defendants.	:	

DECLARATION OF THOMAS K. HEDEMANN IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

I, Thomas K. Hedemann, Esq., declare as follows:

1. I am a member of the bar of the State of Connecticut and an associate at the law firm of Axinn, Veltrop & Harkrider LLP. I am counsel for Defendants Alvogen Pine Brook, Inc. and Alvogen Group, Inc. (collectively, "Alvogen") in Novartis Pharms. Corp. et al. v. Alvogen Pine Brook, Inc., et al., C.A. No. 13-cv-00052-RGA (D. Del.).

2. I submit this declaration in support of Defendants' Motion for Summary Judgment of Noninfringement served herewith.

3. Attached as **Exhibit 1** is a true and correct copy of the May 2, 2014 Covenant not to Sue provided to Alvogen on May 3, 2014.

4. Attached as **Exhibit 2** is a true and correct copy of U.S. Patent No. 6,355,031.

5. Attached as **Exhibit 3** is a true and correct copy of U.S. Patent No. 6,316,023.

6. Attached as **Exhibit 4** is a true and correct copy of ALVRIV00000039-ALVRIV00000040.

7. Attached as **Exhibit 5** is a true and correct copy of Plaintiffs' Initial Infringement Contentions, dated May 28, 2013.

8. Attached as **Exhibit 6** is a true and correct copy of Defendants Alvogen Pine Brook, Inc.'s and Alvogen Group Inc.'s First Set of Interrogatories (Nos. 1-4), dated November 7, 2013.

9. Attached as **Exhibit 7** is a true and correct copy of Plaintiffs' Objections and Responses to Alvogen's First Set of Interrogatories (Nos. 1-4), dated December 9, 2013.

10. Attached as **Exhibit 8** is a true and correct copy of the March 18, 2014 email from C. Coulson to C. Loh.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: May 29, 2014

Thomas K. Hedemann

Exhibit 1

COVENANT NOT TO SUE

WHEREAS Novartis AG and LTS Lohmann-Therapie Systeme AG ("LTS AG") own United States Patent No. 6,316,023 titled "TTS Containing An Antioxidant" ("'023 patent") and United States Patent No. 6,335,031 titled "TTS Containing An Antioxidant" ("'031 patent");

WHEREAS Alvogen Pine Brook, Inc. has submitted Abbreviated New Drug Application ("ANDA") No. [redacted] to the United States Food And Drug Administration seeking approval for Alvogen Pine Brook, Inc. and Alvogen Group, Inc. (collectively, "Alvogen") to engage in the commercial manufacture, use and sale of a [redacted]

NOW THEREFORE:

Novartis AG and LTS AG and their subsidiaries, successors and assigns agree, promise and irrevocably covenant not to sue, assert any claim of infringement of, or otherwise enforce or attempt to enforce the '023 or '031 patents against Alvogen, including each of Alvogen's subsidiaries, officers, directors, employees, customers, distributors, suppliers, representatives and agents, and their successors and assigns, based upon the submission of ANDA No. [redacted] to the United States Food And Drug Administration, or upon the manufacture, use, sale, offer for sale or importation into the United States of the [redacted] dosage strength products that are the subject of and described in ANDA No. [redacted], provided that, in all cases, the [redacted] dosage strength products remain substantially identical to those presently described in ANDA No. [redacted].

This covenant is limited to the '023 and '031 patents, and to the [redacted] dosage strength products that are the subject of and described in ANDA No. [redacted].

Dated: May 2, 2014

By: [signature]

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Exhibit 2

US006335031B1

(12) **United States Patent**
Asmussen et al.

(10) **Patent No.: US 6,335,031 B1**
(45) **Date of Patent: Jan. 1, 2002**

(54) **TTS CONTAINING AN ANTIOXIDANT**

(75) Inventors: **Bodo Asmussen**, Bendorf-Sayn; **Michael Horstmann**, Neuwied, both of (DE); **Kai Köpke**, Triengen (CH); **Henricus L. G. M. Tiemessen**, Weil-Haltingen (DE); **Steven Minh Dinh**, Briarcliff Manor; **Paul M. Gargiulo**, New York, both of NY (US)

(73) Assignees: **Novartis AG**, Basel (CH); **LTS Lohmann Therapie-Systeme GmbH Co. KG**, Neuwied (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/291,498**

(22) Filed: **Apr. 14, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/EP99/00078, filed on Jan. 8, 1999.

(30) **Foreign Application Priority Data**

Jan. 12, 1998 (DE) 9800526

(51) **Int. Cl.**[7] **A61F 13/00**

(52) **U.S. Cl.** **424/449**; 424/448; 602/57; 602/60; 604/290; 604/305; 604/307

(58) **Field of Search** 424/449, 448; 602/57, 60; 604/290, 305, 307

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,602,176 A * 2/1997 Enz 514/490

FOREIGN PATENT DOCUMENTS

FR	2 611 707	9/1988
WO	98/30243	7/1998
WO	98/31356	7/1998

* cited by examiner

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(57) **ABSTRACT**

Pharmaceutical composition comprising (S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in free base or acid addition salt form and an anti-oxidant. Said pharmaceutical compositions may be delivered to a patient using a transdermal delivery device.

20 Claims, No Drawings

TTS CONTAINING AN ANTIOXIDANT

This a continuation-in-part of application PCT/EP99/00078, filed Jan. 8, 1999. The entire contents of the PCT/EP99/00078 disclosure are incorporated herein by reference.

This invention relates to a pharmaceutical composition for systemic administration of a phenyl carbamate, e.g. by transdermal administration. In particular this invention

The polymer, when a hydrophilic polymer, may conveniently take up water and is permeable to water, e.g. moisture from the skin, although the polymer may be insoluble in water. The polymer may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum corneum at a pH of from 4 to 7, preferably at skin pH, e.g. around 5.5. If

(20) sorbitan monooleate, e.g. Tween 80, Registered Trade Mark available from Atlas Chemie, Germany.

3) Polyoxyethylene-(5-40) stearic acid esters, e.g. Myrj (Registered Trade Mark) available from Atlas Chemie, Germany.

4) Polyoxyethylene glycol fatty alcohol ethers, e.g. polyethylene glycol-(6-25) cetyl ether, glycerin polyethylene ricinoleate, glycerin polyethylene glycol stearate (Cremophor brand, Registered Trade Mark available from BASF Germany).

5) Polyoxyethylene glycols of MW from 200 to 600 Daltons, e.g. 300 or 400 Daltons.

6) Esters of poly(2-7)ethylene glycol glycerol ether having at least one hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid, e.g. Polyethylene glycol-(7) glyceryl cocoate, e.g. Cetiol HE, Registered Trade Mark, from Henkel, Germany.

7) Adipic acid lower alkyl esters, e.g. di-n-butyl adipate and diisopropyl adipate.

8) Glycerin polyethylene glycol ricinoleate, e.g. Product of 35 moles ethylene oxide and castor oil, e.g. Brand Cremophor EL Registered Trade Mark, obtainable from BASF, Germany.

9) Triacetin-(1,2,3).

10) Fatty acid, e.g. a C_{12-18} fatty acid.

11) Fatty alcohol, e.g. a C_{12-18} fatty alcohol.

The amount and type of additive required may depend on a number of factors, e.g. the HLB value of the tenside and

d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

In another aspect the present invention provides the use of an anti-oxidant to stabilize a pharmaceutical composition containing Compound A.

Before the finding by the present applicant that an anti-oxidant is necessary in compositions of this invention, it was hitherto thought unnecessary.

The applicant has found that an effective stabilising effect is surprisingly achieved when the antioxidant is selected from tocopherol, esters thereof, e.g. tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably α-tocopherol or ascorbyl palmitate. The antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5%, e.g. 0.05 to 0.20, e.g. 0.15%, more particularly 0.1% by weight based on the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention produced in analogous manner to example 1 described hereinafter containing 0.1% tocopherol show for Example only 1.3% degradation products compared to 4.46% degradation products in equivalent compositions not containing tocopherol in 2 month stress tests at 60° C. Pharmaceutical compositions of the invention in analogous manner to example 1 described

In a preferred embodiment, the backing layer is a double layer which consists of a PET layer as aforementioned and an EVA layer, e.g. Scotch Pack 1012.

The release-liner may be a disposable element which serves to protect the pharmaceutical composition prior to its application. Typically the release-liner is produced from a material impermeable to compound A, and adhesive. This release-liner may be easily stripped away from the adhesive.

the pharmaceutical composition is not exposed to the atmosphere during storage or during application. Such patches further reduce the likelihood of the Compound A being exposed to oxidative influences. The transdermal device may comprise, e.g. a continuous backing layer, a continuous release-liner and located there-between, in discrete portions, a pharmaceutical composition portion, the backing layer being configured such that it may be releasably fixed with

and the part of the body to which the unit is fixed. The amount of and, e.g. area of the composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound.

Orally, the Compound A is well tolerated at an initial dose of 1.5 mg twice a day orally and the dose may be stepped up to 3 mg twice daily in week 2. Higher dosages are possible, for example 4.5 mg twice daily and even 6 mg twice daily. Tolerability is seen to be even better for the transdermal device, wherein 24 mg were absorbed in 24 hours.

The following example illustrates the invention.

EXAMPLE 1

A composition is prepared consisting of the following components (by weight)

	(I)	(II)
Compound A	30%	30%
Polymer	20% (A)	20% (D)
Methacrylate	49.85% (B)	49.85% (C)
α-tocopherol	0.15%	0.15%

The components are added to ethyl acetate and mixed to give a viscous mass. The mass is spread onto a 100 μm transparent PET foil to produce a film 60 μm thick. A 15 μm thick PET foil release-liner is applied onto the dried mass. The patch is cut up into patches 10, 20, 30 or 40 cm^2 in area.

The liner is removed before application to the skin.

The compositions and devices of this invention provide storage stable systems. Insignificant degradation is detected after storage of up to 6 months at room temperature.

EXAMPLE 2

A composition is prepared according to Example 1 with Ascorbyl-palmitate instead of α-tocopherol. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 3

A composition is prepared according to Example 1 with a mixture of Ascorbyl-palmitate and α-tocopherol instead of α-tocopherol alone. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 4

A two-parts composition is prepared consisting of the following components

	Composition per unit (10 cm^2)	
Compound A	18 mg	30%
Polymer	29.94 mg	49.85%
Methacrylate	12 mg	20%
α-tocopherol	0.06	0.1%
Total 1st part (area weight 60 mg/10 cm^2)	70 mg	100%

-continued

	Composition per unit (10 cm^2)	
and		
Bio-PSA Q7-4302	29.67 mg	98.9%
Silicone oil Q7-9120	0.3 mg	1.0%
α-tocopherol	0.03 mg	0.1%
Total 2nd part (area weight 30 mg/10 cm^2)	30 mg	100%

The two parts are then put together in the form of a patch.

What is claimed is:

1. A pharmaceutical composition comprising:
   (a) a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A);
   (b) about 0.01 to about 0.5 percent by weight of an antioxidant, based on the weight of the composition, and
   (c) a diluent or carrier.

2. A pharmaceutical composition according to claim 1 containing 1 to 40% by weight of Compound A in free base or acid addition salt form.

3. A pharmaceutical composition according to claim 1 wherein the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.

4. A pharmaceutical composition according to claim 1 wherein the anti-oxidant is α-tocopherol or ascorbyl palmitate.

5. A pharmaceutical composition according to claim 1 wherein the anti-oxidant is tocopherol and is present in an amount of 0.1% by weight based on the weight of the pharmaceutical composition.

6. A pharmaceutical composition according to claim 1 comprising
   (a) Compound A in free base form in an amount of 20 to 40% by weight,
   (b) polymethacrylate in an amount of 10 to 30% by weight,
   (c) acrylate copolymer in an amount of 40 to 60% by weight, and
   (d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

7. A transdermal device comprising a pharmaceutical composition as defined in claim 1, wherein the pharmaceutical composition is supported by a substrate.

8. A transdermal device according to claim 7, wherein the pharmaceutical composition is located between an adhesive layer and the substrate.

9. A transdermal device according to claim 8, wherein a release liner releasably contacts the adhesive layer.

10. The pharmaceutical composition of claim 1, further comprising silicone oil.

11. A transdermal device comprising a backing layer, a layer comprising a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate (Compound A) and an amount of antioxidant effective to stabilize Compound A from degradation in a polymer matrix, a release-liner and, disposed between the layer comprising Compound A in a polymer matrix and the release-liner, a discrete layer of adhesive material for releasably fixing said transdermal device to a patient's skin.

12. The transdermal device of claim 1, wherein the discrete layer of adhesive material also comprises silicone oil.

13. The transdermal device of claim 1, wherein the antioxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, or propyl gallate.

14. The transdermal device of claim 1, wherein the antioxidant is α-tocopherol or ascorbyl palmitate.

15. A method of stabilizing (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A), wherein the method comprises forming a composition by combining Compound A with an amount of anti-oxidant effective to stabilize Compound A from degradation.

16. A method according to claim 15, wherein the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.

17. The method of claim 15, wherein the anti-oxidant is α-tocopherol or ascorbyl palmitate.

18. The method of claim 15, wherein the anti-oxidant is present in an amount of from about 0.01 to about 0.5% by weight based on the weight of the composition.

19. The method of claim 15, wherein α-tocopherol is present as the antioxidant in an amount of 0.1% by weight of the composition.

20. The method of claim 15, wherein the composition also comprises silicone oil.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,335,031 B1
DATED : January 1, 2002
INVENTOR(S) : Asmussen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [30], should read:
-- Jan. 12, 1998 (GB) ..... 9800526 --.

Item [56], **References Cited**, U.S. PATENT REFERENCES, should read:

-- 4,948,807	8/1990	Rosin et al.	514/484
5,344,656	9/1994	Enscore et al.	424/448
5,462,745	10/1995	Enscore et al.	424/448 --

Item [56], **References Cited**, FOREIGN PATENT REFERENCES, should read:

-- EP	427 741 B1	5/1991
WO	89/12470	12/1989 --

Column 9,
Lines 1-3, should read:

-- The transdermal device of claim 11, wherein the discrete layer of adhesive material also comprises silicone oil. --.
Lines 4-7, should read:

-- The transdermal device of claim 11, wherein the antioxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, or propyl gallate. --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,335,031 B1
DATED : January 1, 2002
INVENTOR(S) : Asmussen et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 9, cont'd.
Lines 8-9, should read:

-- The transdermal device of claim 11, wherein the antioxidant is α-tocopherol or ascorbyl palmitate. --.

Signed and Sealed this

First Day of October, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

Exhibit 3

US006316023B1

(12) **United States Patent**
Asmussen et al.

(10) **Patent No.: US 6,316,023 B1**
(45) **Date of Patent: *Nov. 13, 2001**

(54) **TTS CONTAINING AN ANTIOXIDANT**

(75) Inventors: **Bodo Asmussen**, Bendorf-Sayn; **Michael Horstmann**, Neuwied, both of (DE); **Kai Köpke**, Triengen (CH); **Henricus L. G. M. Tiemessen**, Weil-Haltingen (DE); **Steven Minh Dinh**, Briarcliff Manor; **Paul M. Gargiulo**, New York, both of NY (US)

(73) Assignees: **Novartis AG**, Basel (CH); **LTS Lohmann Therapie-Systeme GmbH**, Neuwied (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/747,519**

(22) Filed: **Dec. 20, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/291,498, filed on Apr. 14, 1999, which is a continuation-in-part of application No. PCT/EP99/00078, filed on Jan. 8, 1999.

(30) **Foreign Application Priority Data**

Jan. 12, 1998 (GB) 9800526

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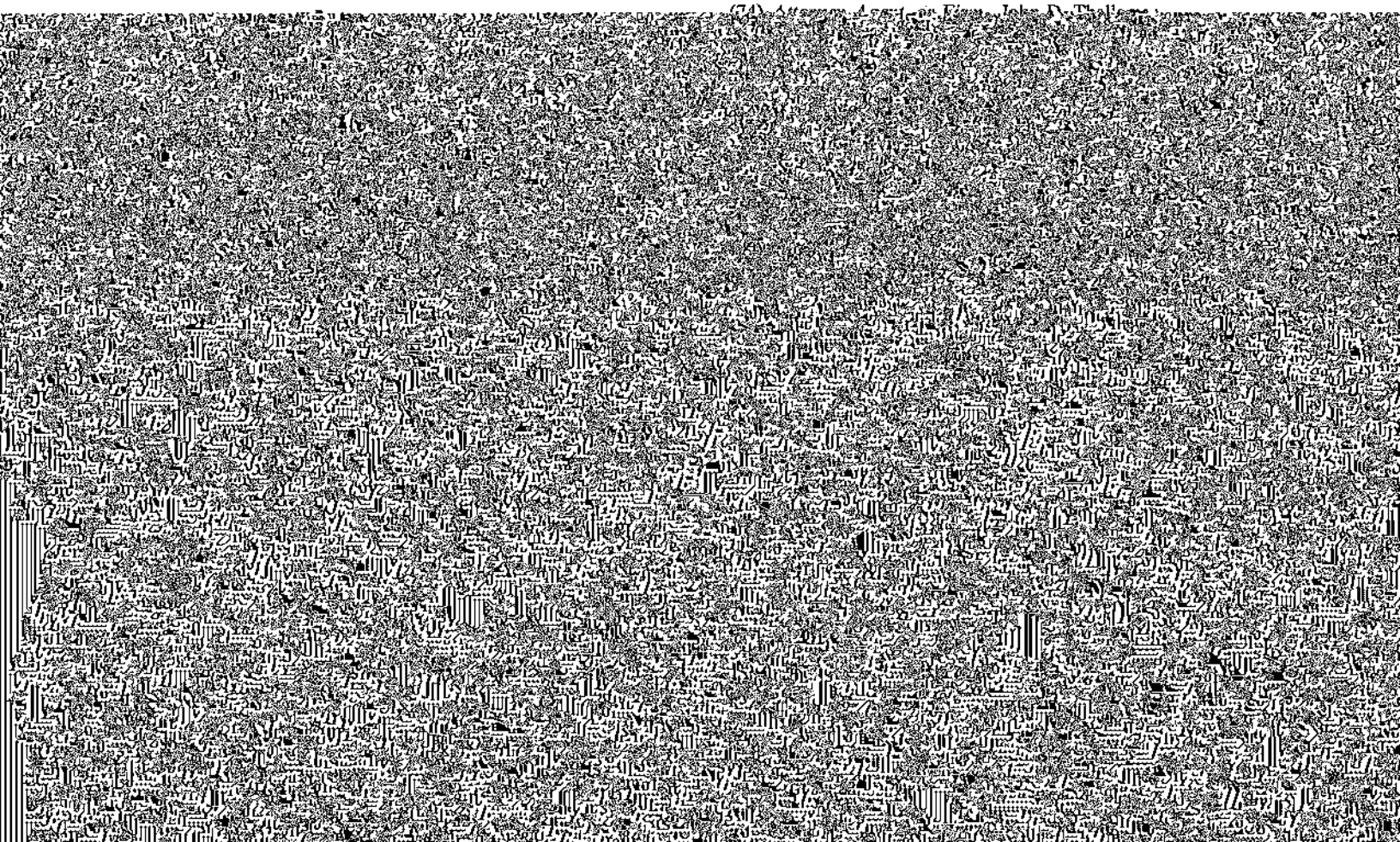
Primary Examiner—S. Mark Clardy
Assistant Examiner—Michael A. Williamson



TTS CONTAINING AN ANTIOXIDANT

This application is a continuation of U.S. application Ser. No. 09/291,498, filed Apr. 14, 1999, which is a continuation-in-part of International Application No. PCT/EP99/00078, filed Jan. 8, 1999.

This invention relates to a pharmaceutical composition for systemic administration of a phenyl carbamate, e.g. by transdermal administration. In particular this invention relates to a pharmaceutical composition of the phenyl carbamate—(S)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate—(hereinafter referred to as compound A) in free base or acid addition salt form as disclosed in published UK patent application GB 2 203 040, the contents of which are incorporated herein by reference.

Compound A is useful in inhibiting acetylcholinesterase in the central nervous system, e.g. for the treatment of Alzheimer's disease.

A transdermal composition in the form of a patch is described in Example 2 of GB 2,203,040 according to which compound A is mixed with two polymers and a plasticiser to form a viscous mass. This mass is applied to a foil which is cut into patches.

It has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen. The transdermal composition described in GB 2203040 has been found to degrade, possibly by oxidative degradation, despite the formation of an occlusive polymer matrix around compound A and its storage in air-tight packaging.

The present applicant has found that stable pharmaceutical compositions comprising compound A can now be obtained, which show insignificant degradation of compound A over a prolonged time period, e.g. 2 years, as indicated by standard tests, e.g. stress tests.

In one aspect, the invention provides a pharmaceutical composition comprising Compound A in free base or acid addition salt form and an anti-oxidant.

The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests.

The pharmaceutical compositions of the invention may contain high amounts of compound A, e.g. from 1 to 40% by weight, e.g. 10–35%, more particularly 20–35%, e.g. 30%.

The compound A may be in any of a wide variety of pharmaceutical diluents and carriers known in the art. The diluent or carrier may contain trace amounts of free radicals without affecting the stability of the pharmaceutical composition of the invention.

The diluent or carrier is preferably one or more polymers, more preferably a hydrophilic polymer or polymers. In a preferred embodiment the diluent of carrier is selected from at least one polymer selected from acrylate polymers, and polymethacrylate polymers. The polymers preferably have a mean molecular weight of from about 50,000 to about 300,000 Daltons, e.g. 100,000 to 200,000 Daltons. The polymers preferably are capable of forming a film, thus to be compatible to the skin.

As a polymer one can mention in particular an acrylate co-polymer, e.g. co-polymers of butyl acrylate, ethyl hexyl acrylate and vinyl acetate. Preferably the polymer is cross-linked. A preferred acrylate polymer is one of the Durotak brand available from National Starch and Chemical Company, Zutphen, Holland, e.g. Durotak 87-2353 (hereinafter polymer A), 387-2051 or 387-2052 (hereinafter polymer D).

The diluent or carrier is preferably present in an amount of up to 90%, more preferably 70% by weight base on the total weight of the pharmaceutical composition.

The polymer, when a hydrophilic polymer, may conveniently take up water and is permeable to water, e.g. moisture from the skin, although the polymer may be insoluble in water. The polymer may swell and provide release of a large amount of pharmacologically active agent leading to a high concentration gradient of pharmacologically active agent between the skin surface and stratum corneum at a pH of from 4 to 7, preferably at skin pH, e.g. around 5.5. If desired such polymers may be soluble in organic solvents.

Examples of suitable polymers include polyacrylamide and its co-polymers, polyvinylpyrrolidone (PVP), vinyl acetate/vinyl alcohol co-polymers, polyvinyl alcohol (PVA) and derivatives, ethyl cellulose and other cellulose and starch derivatives.

Hydrophilic polyacrylates are preferred polymers. The polyacrylate may be substituted, e.g. a methacrylate. They may be commercially available acrylate/methacrylate co-polymers. Some or all of the acid groups may be esterified, e.g. with alkyl (C_{1-10}) groups, more particularly alkyl groups having 1 to 4 carbon atoms such as methyl or ethyl groups.

Examples of commercially available polymers of this type include:

1) Polymers of methacrylate containing alkyl (C_{1-4}) ester groups. Preferably the polymer matrix is a mixture of an acrylate polymer and a methacrylate polymer e.g. in a weight ratio of from 5:1 to 1:1, e.g. 4:1 to 2:1 e.g. 3:1, e.g. butylmethylacrylate and methylmethylacrylate. MW 20000, e.g. Plastoid B from Röhm, Darmstadt, Germany (hereinafter polymer B).
2) Polymers of acrylate and methacrylate esters containing methyl and ethyl neutral ester groups and trimethylaminoethyl cationic ester groups. Chloride ions may be present. Mean Molecular weight 150000 Daltons. Viscosity (20° C.), maximum 15 cP. Refractive index 1.380–1.385. Density 0.815–0.835 g/cm^3. Ratio of cationic ester groups to neutral alkyl groups 1:20 giving an alkali count of 28.1 mg KOH per gram polymer (Eudragit RL 100 Registered Trade Mark available from Röhm) or 1:40 giving an alkali count of 15.2 mg KOH per gram polymer (Eudragit RS 100 Registered Trade Mark, also available from Röhm).
3) Polymers of methacrylate esters containing trimethylaminoethyl cationic ester groups and other neutral (C_{1-4})alkyl ester groups. Chloride ions may be present. Mean molecular weight 150,000. Viscosity (20° C.) 10 cP. Refractive Index 1.38. Density 0.815. Alkali number of 180 mg KOH per gram polymer (Eudragit E 100, Registered Trade Mark, also available from Röhm and hereinafter referred to a polymer C).

If desired the pharmaceutical composition may contain other additives, such as plasticizers and/or softeners preferably skin compatible tensides, e.g. to provide flexibility to the pharmaceutical composition, and/or to dissolve partially or totally compound A.

Examples of additives include:

1) Polyoxyethylene fatty alcohol ethers. The alcohol may e.g. be a C_{12-18} alcohol. The HLB value may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(10) oleyl ether. A suitable ether may have a viscosity (25° C.) of about 100 cP, a solidification point of about 16° C., an HLB value of 12.4 and an acid count maximum 1.0 (Brij 97 Registered Trade Mark available from Atlas Chemie, Germany).
2) Polyoxyethylene Sorbitan fatty acid esters. The fatty acid may be e.g. a C_{12-18} fatty acid. The HLB value

may be e.g. from 10 to 18. A preferred example is polyoxyethylene-(20) sorbitan monooleate, e.g. Tween 80, Registered Trade Mark available from Atlas Chemie, Germany.

3) Polyoxyethylene-(5-40) stearic acid esters, e.g. Myrj (Registered Trade Mark) available from Atlas Chemie, Germany.

4) Polyoxyethylene glycol fatty alcohol ethers, e.g. polyethylene glycol-(6-25) cetyl ether, glycerin polyethylene ricinoleate, glycerin polyethylene glycol stearate (Cremophor brand, Registered Trade Mark available from BASF Germany).

5) Polyoxyethylene glycols of MW from 200 to 600 Daltons, e.g. 300 or 400 Daltons.

6) Esters of poly(2-7)ethylene glycol glycerol ether having at least one hydroxyl group and an aliphatic (C_{6-22}) carboxylic acid, e.g. Polyethylene glycol-(7) glyceryl cocoate, e.g. Cetiol HE, Registered Trade Mark, from Henkel, Germany.

7) Adipic acid lower alkyl esters, e.g. di-n-butyl adipate and diisopropyl adipate.

8) Glycerin polyethylene glycol ricinoleate, e.g. Product of 35 moles ethylene oxide and castor oil, e.g. Brand Cremophor EL Registered Trade Mark, obtainable from BASF, Germany.

9) Triacetin-(1,2,3).

10) Fatty acid, e.g. a C_{12-18} fatty acid.

11) Fatty alcohol, e.g. a C_{12-18} fatty alcohol.

The amount and type of additive required may depend on a number of factors, e.g. the HLB value of the tenside and the flexibility of the pharmaceutical required. The amount of additive does not significantly influence the capability of the polyacrylate to form films. Generally the weight ratio of tenside to the polymer may be from about 1:10 to 5:1, e.g. 1:10 to 1:3.

Preferably, however, no such additive is present or is only present in an amount less than 1% by weight based on the total weight of the pharmaceutical composition.

The pharmaceutical composition may contain skin penetration promoters, e.g. 1-dodecylazacycloheptan-2-one (azone) and N,N-diethyl-m-toluamide (DEET).

The amount and type of skin penetration promoter, and/or additives present may depend on a number of factors. Generally the weight ratio of skin penetration promoting agent to hydrophilic polymer will be from about 1:1 to 1:10. Preferably the amount of tenside and/or skin penetration promoter may be from about 3 to about 50%, preferably 20 to 40% by weight of the pharmaceutical composition.

Preferably however no such additive is present or is only present in an amount less than 1% by weight of the pharmaceutical composition.

If desired the pharmaceutical composition may contain a hydrophobic elastomer, e.g. a synthetic resin. Such resins are conventional in the plaster art. Suitable resins may include non-swellable acrylate resins. These may if desired be adhesive. The weight ratio of polymer, e.g. hydrophilic polymer to resin may for example be from 1:0.5 to 1:10. The resin may contain modifiers, extenders, e.g. of softening point about 50 to 100° C. Such extenders may have adhesive or softening properties. Examples of such extenders may include resin acids, glyceryl and phthalate esters of resin acids.

A preferred pharmaceutical composition according to the invention comprises

b) polymethacrylate in an amount of 10 to 30% by weight

c) acrylate copolymer in an amount of 40 to 60% by weight, and

d) α-tocopherol in an amount of between 0.05 and 0.3% by weight

wherein the total weight of the pharmaceutical composition is 100%.

In another aspect the present invention provides the use of an anti-oxidant to stabilize a pharmaceutical composition containing Compound A.

Before the finding by the present applicant that an anti-oxidant is necessary in compositions of this invention, it was hitherto thought unnecessary.

The applicant has found that an effective stabilising effect is surprisingly achieved when the anti-oxidant is selected from tocopherol, esters thereof, e.g. tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate, preferably α-tocopherol or ascorbyl palmitate. The antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5%, e.g. 0.05 to 0.20, e.g. 0.15%, more particularly 0.1% by weight based on the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention produced in analogous manner to example 1 described hereinafter containing 0.1% tocopherol show for Example only 1.3% degradation products compared to 4.46% degradation products in equivalent compositions not containing tocopherol in 2 month stress tests at 60° C. Pharmaceutical compositions of the invention in analogous manner to example 1 described hereinafter containing 0.15% tocopherol show for example only 0.25% degradation products compared to 1.09% degradation products in compositions not containing tocopherol in 3 month stress tests at 40° C. at 75% room humidity.

The pharmaceutical composition of the invention is preferably used for transdermal application.

In another aspect of the invention there is provided a transdermal device for administering a Compound A which comprises a pharmaceutical composition containing Compound A, a backing layer providing support for the pharmaceutical composition, an adhesive for fixing the pharmaceutical composition to the backing layer and a release-liner releasably contacting said adhesive.

The pharmaceutical composition may be conveniently contained in a discrete thin layer, the upper and lower surfaces of which may be coated in a layer of adhesive the surface of which in turn provide backing layer and release-liner contacting surfaces.

The pharmaceutical composition contained in the discrete layer may comprise the Compound A and other excipients in a polymer matrix, the polymer matrix therefor being provided by the diluent or carrier aforementioned. If desired Compound A may be dispersed throughout, or dissolved in, said polymer matrix.

The transdermal device may alternatively be of a more simple construction wherein the polymer matrix containing the pharmaceutical composition additionally comprises an adhesive. In such a simple construction there is no need for the layers of the aforementioned adhesive in order to fix and releasably fix respectively the backing layer and release-liner as the polymer matrix containing the Compound A is self adhesive.

The thickness of the pharmaceutical composition layer in a transdermal device may be in the order of from 20 to 100

enough to resist wrinkling which may arise upon prolonged periods in storage and through the movement of a subject's skin. Typically, the backing layer is, e.g. from approximately 10 μm to 15 μm, in thickness.

In a preferred embodiment, the backing layer is a double layer which consists of a PET layer as aforementioned and an EVA layer, e.g. Scotch Pack 1012.

The release-liner may be a disposable element which serves to protect the pharmaceutical composition prior to its application. Typically the release-liner is produced from a material impermeable to compound A, and adhesive. This release-liner may be easily stripped away from the adhesive. A preferred release-liner is made of poly(ethylene terephthalate) PET foil. A release-liner, e.g. of about 50 to 250 μm, e.g. 100 μm thickness PET film, may be applied over the pharmaceutical composition.

The release liner may be silicone-coated. Said coating is preferably formed of any fluorosilicone compound which is conventionally used in the art, e.g a polyfluoroalkylsiloxane.

It is particularly preferred to employ such a fluorosilicone coating when the adhesive used to affix the pharmaceutical composition to the release liner is not itself a silicone adhesive.

The adhesive may be chosen from any adhesive suitable for skin contact and is preferably an adhesive in which Compound A dissolves at least partly. Preferably the adhesive is a contact adhesive which is pressure sensitive. Preferred adhesive are chosen from amine-resistant silicone pressure sensitive adhesives known in the art, for example the BIO-PSA adhesives produced by Dow Corning Corporation, in particular BIO-PSA Q7-4302.

In a very simple construction of the transdermal device, the adhesive may in fact be the polymer of the polymer matrix.

In a further embodiment, the invention provides a transdermal device comprising a backing layer, a layer comprising compound A in a polymer matrix, a release-liner and, disposed between the layer comprising compound A in a polymer matrix and the release liner, a discrete layer of adhesive material for releasably fixing said transdermal device to patients skin.

Preferably, the adhesive material is a silicone adhesive chosen from amine-resistant silicone pressure sensitive adhesives as hereinabove described.

Typically, a transdermal device of said further embodiment comprises:

a) a polymethacrylate backing layer

b) Compound A in free base form in an acrylate copolymer

c) a BIO-PSA Q7-4302 silicone adhesive layer

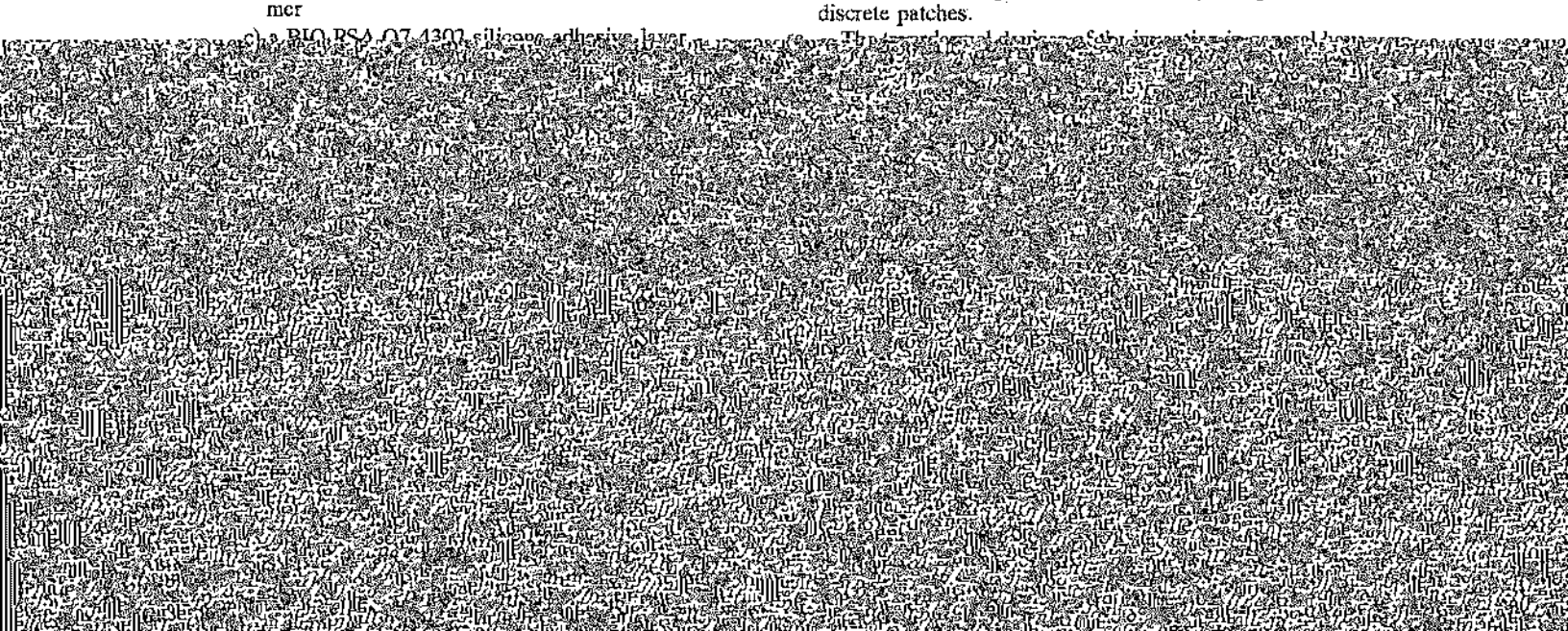
ceutical composition-containing layer of the laminate to the atmosphere at the outer edges of the patch.

In an alternative embodiment, however, a transdermal device is provided wherein in the patches formed therefrom, the pharmaceutical composition is not exposed to the atmosphere during storage or during application. Such patches further reduce the likelihood of the Compound A being exposed to oxidative influences. The transdermal device may comprise, e.g. a continuous backing layer, a continuous release-liner and located there-between, in discrete portions, a pharmaceutical composition portion, the backing layer being configured such that it may be releasably fixed with an adhesive to the release-liner so to seal said pharmaceutical composition in a pocket defined by the inner surface of the backing layer and inner surface of the release-liner. This embodiment may be conveniently referred to as a cover patch.

The pocket described hereinabove is preferably filled with an adhesive so as to encapsulate completely the discrete portion of pharmaceutical composition. Preferably the adhesive is a silicone pressure sensitive adhesive as described hereinabove.

It is an optional feature of all the transdermal devices described hereinabove that they comprise a layer of adhesive between the pharmaceutical composition and the release liner. This, has the primary function of fixing the release liner in contact with the remainder of the device thus protecting the pharmaceutical composition before use. However, if the adhesive is a silicone adhesive, then the layer may additionally act as a membrane through which the Compound A may pass at a controlled rate into the patient through the skin. Without wishing to be limited to a particular theory, it is suggested that the Compound A, dispersed throughout the polymer matrix exhibits little tendency to migrate into the silicone adhesive layer during storage. Accordingly, there is relatively low concentration of Compound A in the silicone layer. In use, the subjects skin, however, may display a much higher affinity for Compound A than the silicone layer and the initial low concentration of Compound A in the silicone layer passes into the subject's body. The silicone layer surprisingly prevents the subject from receiving a sudden high dose of Compound A upon application of the device and instead promotes a gradual increase of concentration in the subject.

The cover patch transdermal device may conveniently be formed as a continuous sheet or webbing and may be cut, or torn along a frangible area dividing each device, into patches before use although such devices may be provided as discrete patches.



drug release characteristics of the compositions, the drug penetration rate observed in vitro and in vivo tests, the duration of action required, the form of compound A, and for transdermal compositions the size of the skin contact area, and the part of the body to which the unit is fixed. The amount of and, e.g. area of the composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound.

Orally, the Compound A is well tolerated at an initial dose of 1.5 mg twice a day orally and the dose may be stepped up to 3 mg twice daily in week 2. Higher dosages are possible, for example 4.5 mg twice daily and even 6 mg twice daily. Tolerability is seen to be even better for the transdermal device, wherein 24 mg were absorbed in 24 hours.

The following example illustrates the invention.

EXAMPLE 1

A composition is prepared consisting of the following components (by weight)

	(I)	(II)
Compound A	30%	30%
Polymer	20% (A)	20% (D)
Methacrylate	49.85% (B)	49.85% (C)
α-tocopherol	0.15%	0.15%

The components are added to ethyl acetate and mixed to give a viscous mass. The mass is spread onto a 100 μm transparent PET foil to produce a film 60 μm thick. A 15 μm thick PET foil release-liner is applied onto the dried mass. The patch is cut up into patches 10, 20, 30 or 40 cm^2 in area.

The liner is removed before application to the skin.

The compositions and devices of this invention provide storage stable systems. Insignificant degradation is detected after storage of up to 6 months at room temperature.

EXAMPLE 2

A composition is prepared according to Example 1 with Ascorbyl-palmitate instead of α-tocopherol. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 3

A composition is prepared according to Example 1 with a mixture of Ascorbyl-palmitate and α-tocopherol instead of α-tocopherol alone. Insignificant amounts of degradation products are detected after storage of at least four months at room temperature.

EXAMPLE 4

A two-parts composition is prepared consisting of the following components

	Composition per unit (10 cm^2)	
Compound A	18 mg	30%
Polymer	29.94 mg	49.85%
Methacrylate	12 mg	20%
α-tocopherol	0.06	0.1%
Total 1st part (area weight 60 mg/10 cm^2) and	70 mg	100%
Bio-PSA Q7-4302	29.67 mg	98.9%
Silicone oil Q7-9120	0.3 mg	1.0%
α-tocopherol	0.03 mg	0.1%
Total 2nd part (area weight 30 mg/10 cm^2)	30 mg	100%

The two parts are then put together in the form of a patch.

What is claimed is:

1. A pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

2. The composition according to claim 1 wherein the antioxidant is selected from the group consisting of tocopherol, esters of tocopherol, ascorbic acid, esters of ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, propyl gallate, and combinations thereof.

3. The composition according to claim 2 wherein the antioxidant is α-tocopherol or ascorbyl palmitate.

4. The composition according to claim 1 wherein the antioxidant is present in an amount of from 0.05 to 0.2 weight percent.

5. The composition according to claim 4 wherein the antioxidant is present in an amount of from 0.1 to 0.15 weight percent.

6. A pharmaceutical composition comprising 7 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base; 10 to 30 weight percent of polymethacrylate or acid addition salt; 0.05 to 0.3 weight percent of α-tocopherol, wherein the weight percents are based on the total weight of the composition.

7. A transdermal device comprising a pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

8. The transdermal device according to claim 7 further comprising an antioxidant; a backing layer providing support for the pharmaceutical composition; an adhesive for contacting and fixing the pharmaceutical composition to the backing layer; and a release liner releasably contacting said adhesive.

9. The transdermal device according to claim 7 comprising a backing layer; a layer comprising (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate and an antioxidant in a polymer matrix; a release liner; and an adhesive layer between the layer comprising (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in a polymer matrix and the release liner, wherein the adhesive layer releasably fixes the transdermal device to a patients skin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,316,023 B1
DATED : November 13, 2002
INVENTOR(S) : Asmussen et al.

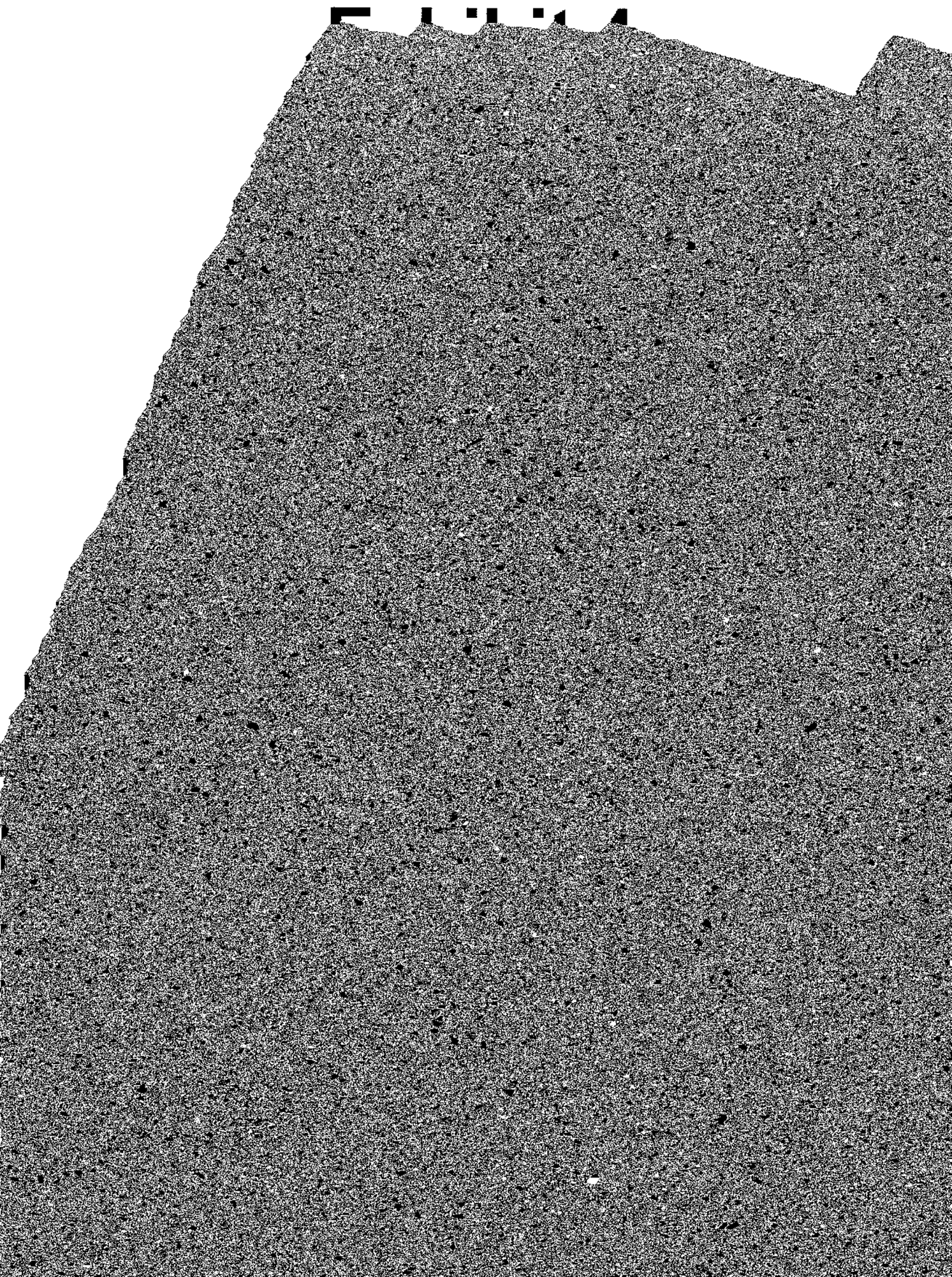
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8,
Line 1, should read -- A pharmaceutical compostion comprising 20 to 40 --.
Line 3, should read -- Ethyl-3-[(1dimethylamino)ethyl]-N-methylphenyl carba- --.
Line 4, should read --mate in the form of a free base or acid addition salt, 0.01 to --.

Signed and Sealed this

Twenty-fifth Day of March, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office



[redacted]

m1
ADMINISTRATIVE

1.12.12 COMPARISON OF GENERIC DRUG AND REFERENCE LISTED DRUG

1. Conditions of use, active ingredient, route of administration, dosage form and strength

As required by 21 CFR §314.94(a) and 505(j)(2)(i), the following information is provided to demonstrate that the conditions of use, active ingredient, component ingredients (as appropriate), route of administration, dosage form and strength of the proposed drug are the same as that of the reference listed drug.

[redacted]

(1)From RLD package insert. Refer to package insert in [redacted] Please note the RLD Labeling does not provide a full and complete list of the inactive ingredients.
* Removed during the manufacturing process and is not present in the final product

The labeling of the proposed drug and the reference listed drug upon which this application is based are the same with the exception of those differences required because the proposed drug product and reference listed drug product are produced/distributed by different manufacturers and wording covered by patent protection and/or exclusivity. All exceptions are annotated on the side-by-side labeling comparison

[redacted]

[redacted]

m1
ADMINISTRATIVE

in electronic format provided in [redacted]

The *in vitro* release rate, comparing the innovator's Exelon® Patch (Rivastigmine Transdermal System, 4.6 mg/24hr and 9.5 mg/24 hr) with the [redacted] s included in this module.

[redacted]

Exhibit 5

Exhibit 6

Exhibit 7

Exhibit 8

From:	Coulson, Chris
To:	"CLoh@fchs.com"; "NKallas@fchs.com"; "FPrugo@fchs.com"
Cc:	"CAT@pgslaw.com"; "MKelly@McCarter.com"; "blemon@McCarter.com"; Landmon, Chad A.; Hedemann, Thomas K.; Russell, Thara L.; slee@kenyon.com; Hardman, Cynthia Lambert; Schreiber, Eric; mch@pgslaw.com; jcp@pgslaw.com; "DGattuso@proctorheyman.com"; "dsilver@mccarter.com"
Subject:	RE: Novartis v. Alvogen C.A. No. 13-00052-RGA (consolidated) and Novartis v. Noven C.A. No. 13-00527-RGA
Date:	Tuesday, March 18, 2014 10:20:26 AM

Dear Chris,

I write on behalf of Defendants to document our meet-and-confer held yesterday regarding certain deficiencies in Plaintiffs' discovery as set forth in Defendants' February 27 and March 11 letters.

First, we have reached an impasse regarding much of this discovery. Regarding Plaintiffs' objections to Defendants' Rule 30(b)(6) notice to Novartis and LTS as addressed in Defendants' February 27 letter, we understand that Plaintiffs stand by their objections regarding Topics 5-9, 11-13, 17-19, and 28, and the parties have reached an impasse regarding these Topics.

With respect to Topics 5-8 (factual basis for infringement allegations), you represented during the meet-and-confer that, as of today, Novartis and LTS do not possess any information beyond what is disclosed in Plaintiffs' infringement contentions and interrogatory responses. Further, you could not identify a factual basis for asserting that any specific ingredient, component or portion of either Alvogen's or Noven's ANDA Products literally infringe the "antioxidant" limitation of the asserted claims, beyond referring Defendants to your contentions and interrogatory responses.

Regarding Defendants' March 11 letter, I understand that we have reached an impasse as to the discovery documented in sections I ([redacted] and II [redacted] of the letter. Regarding section III, I understand based on our meet-and-confer that Plaintiffs are maintaining their objections to RFP Nos. 51-59 and 63 and that we have reached an impasse regarding these RFP's.

We are disappointed that we were unable to narrow the above dispute in that Plaintiffs stand by each and every one of their objections to this discovery. Defendants consider these matters ripe for resolution by the Court, and reserve the rights to seek all appropriate remedies and relief, including the right to re-depose Plaintiffs.

Second, regarding Section III of Defendants' March 11 letter, thank you for agreeing that Plaintiffs would reconsider their subpart objection and advise us whether Plaintiffs will provide a response to Noven's Interrogatory Nos. 12-15 and 17, by this Wednesday. As I explained on the call, Plaintiffs' deposition is scheduled for March 27 and Defendants need Plaintiffs' substantive responses to this discovery as soon as possible, but no later than within this week.

Third, please provide the name of Plaintiffs' deposition witness as soon as possible. You told me that a witness had been identified, but you could not recall the witnesses' name on the call. Please provide this information, and a proposed deposition start time for the March 27 deposition, as soon as possible.

Chris Coulson
Kenyon & Kenyon LLP
Tel: 212.908.6409

Exhibit D

DEFENDANTS' MOTION FOR LEAVE TO FILE
A MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG,	:	C.A. No. 1:13-cv-00052-RGA
Plaintiffs,	:	
v.	:	
ALVOGEN PINE BROOK, INC. and ALVOGEN GROUP, INC.,	:	
Defendants.	:	

ORDER

THIS MATTER, having come before the Court on the Motion of Defendants Alvogen Pine Brook, Inc. and Alvogen Group, Inc. (collectively "Alvogen"), by counsel, Proctor Heyman LLP and Axinn, Veltrop & Harkrider LLP, for the entry of an Order granting Defendants' Motion for Summary Judgment of Noninfringement, said motion pertaining to Alvogen's Abbreviated New Drug Application for a rivastigmine transdermal system, 4.6 mg/24 hr and 9.5 mg/24 hr dosage strengths, and the Court having consider the papers submitted in support of the Motion, and for good cause shown;

IT IS on this _____day of _____, 2014;

ORDERED that Defendants' Motion for Summary Judgment of Noninfringement be and hereby is **GRANTED**.

_____
Honorable Richard G. Andrews, U.S.D.J